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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>3</sup> :</b> <b>A61K 9/62, 9/28, 9/32</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 84/ 00296</b> <b>(43) International Publication Date:</b> 2 February 1984 (02.02.84)
<b>(21) International Application Number:</b> PCT/US83/01041 <b>(22) International Filing Date:</b> 8 July 1983 (08.07.83) <b>(31) Priority Application Number:</b> 396,668 <b>(32) Priority Date:</b> 9 July 1982 (09.07.82) <b>(33) Priority Country:</b> US  <b>(71) Applicant:</b> KEY PHARMACEUTICALS, INC. [US/ US]; 18425 N.W. 2nd Avenue, Miami, FL 33169 (US). <b>(72) Inventors:</b> KEITH, Alec ; 539 Beaumont Drive, State College, PA 16801 (US). HSIAO, Charles ; 4890 104th Avenue, Cooper City, FL 33328 (US). <b>(74) Agents:</b> WEGNER, Harold C. et al.; Wegner & Bretschneider, 2000 L Street, N.W., Suite 425, Wash- ington, DC 20036-0542 (US).		<b>(81) Designated States:</b> AT (European patent), BE (Euro- pean patent), CH (European patent), DE (European patent), FR (European patent), GB (European pa- tent), JP, LU (European patent), NL (European pa- tent), SE (European patent).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> QUINIDINE SUSTAINED RELEASE DOSAGE FORMULATION		
<b>(57) Abstract</b>  A sustained release oral dosage form comprising a tablet core containing a pharmaceutically effective amount of quinidine. The tablet core is coated with a sustained release polymeric coating which contains about 5 to about 20 percent by weight polyethylene glycol component having a molecular weight of from about 500 to about 2000, and from about 80 to 95 percent by weight polyvinylalcohol component. The polyvinylalcohol component comprises from about one to about ten parts by weight of a partially hydrolyzed polyvinylalcohol subcomponent having a degree of hydrolysis of from about 75 to about 92 percent and about one part by weight of a substantially completely hydrolyzed polyvinylalcohol subcomponent having a degree of hydrolysis in excess of 95%.		

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QUINIDINE SUSTAINED RELEASE DOSAGE FORMULATIONSummary of the Invention

Quinidine is a well known alkaloid used in the treatment of certain cardiac arrhythmias. It is a general cardiac depressant, which reduces myocardial excitability, automaticity and conductivity.

In accordance with the invention, there is provided a sustained release oral dosage form which provides a patient with quinidine over a prolonged period of time. The dosage form comprises a tablet core containing a pharmaceutically effective amount of quinidine. The tablet core is coated with a sustained release polymeric coating which contains from about 5 to about 20 percent by weight polyethylene glycol component having a molecular weight of from about 500 to about 2000, and from about 80 to about 95 percent by weight polyvinylalcohol component.

The polyvinylalcohol component comprises from about one to about ten parts by weight of a partially hydrolyzed polyvinylalcohol subcomponent, with a degree of hydrolysis of about 75 to about 92 percent; and about one part by weight of a substantially completely hydrolyzed polyvinylalcohol subcomponent having a degree of hydrolysis in excess of 95%.

Detailed Description of the Invention

The invention provides a sustained release formulation with an increased residency time in the gastrointestinal tract, and one where the rate of partial or total dissolution of the sustained release polymeric coating can be controlled through adjustment of the ratio of the polyvinylalcohol subcomponents. In a comparison to components with a lower ratio of the partially hydrolyzed to substantially completely hydrolyzed polyvinylalcohol, the sustained release dosage form with a higher ratio will move more slowly through



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the gastrointestinal tract during the period of structural integrity of the sustained release polymeric coating. However, the period of structural integrity will be relatively short. Conversely, with a ratio approaching an even mixture of the two subcomponents, the structural integrity will be maintained for a longer period of time, but with a faster passage of the sustained release dosage form through the gastrointestinal tract.

In accordance with a preferred aspect of the invention, a ratio of from about 6:1 to about 2:1 of the partially hydrolyzed to substantially completely hydrolyzed components is contemplated, with a more preferred aspect of the invention providing said ratio as about 4:1.

The tablet core in a generic aspect of the invention may include a conventional tablet that is coated with the sustained release polymeric coating of the invention. In accordance with a preferred aspect of the invention, the tablet core is made of compressed granules each having a mesh size smaller than about 12 mesh, the granules being made of, for example, methylcellulose and lactose containing the quinidine.

Quinidine is defined to include any of the pharmaceutically acceptable forms of quinidine, with quinidine bisulfate as a preferred embodiment.

The sustained release polymeric coating is preferably applied through an air suspension coating technique (e.g., a six inch Wurster column manufactured by Glatt Air Techniques is satisfactory for the invention). The tablet cores are suspended in the air suspension column and coated with a spray of the polymeric mixture comprising the sustained release polymeric coating.

The total amount of quinidine should, when quinidine bisulfate is used as the form of quinidine, comprise from about 100 to about 400 mg per finished oral



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sustained release dosage form, with about 300 mg being contemplated in one embodiment.

The prolonged period of time will vary based upon the ratio of the polyvinylalcohol subcomponents. In accordance with a preferred aspect of the invention, a sustained release for a period of at least about 8 hours is contemplated, and in a still more preferred embodiment a release over a period of 12 hours. With a sustained release over a period of 12 hours, taking into account the half-life of the drug, the patient is provided with systemic activity at a suitable rate for a period of at least about 24 hours.

The following example illustrates the invention:

900 gm quinidine bisulfate, 300 gm of methyl cellulose (Methocel E-50, Dow) and 600 gm lactose are mixed together and granulated with 60 ml of a 2% solution of Methocel R-50. The granulation was tray-dried in a 50°C oven for a period of 16 hours and passed through a 12 mesh screen. The resulting granulation mixture is admixed with one percent magnesium stearate and compressed into 610 mg tablet cores, each of the cores containing 300 mg quinidine bisulfate. 1000 gm of the the tablet cores are placed in a six inch Wurster air suspension coating column and a fluidized bed of the granulation mixture is created through conventional air suspension technique. While so suspended in the fluidized bed, a coating mixture of 1400 ml of a polyvinylalcohol solution which contains 54.2 gm of polyvinylalcohol, mw 76,000, 88% hydrolyzed (Mowiol 18-88, Hoechst), and 13.60 gm polyvinylalcohol, mw 115,000, 100% hydrolyzed is introduced. The process utilized an inlet air temperature of 70°C, a spray pressure of 2 bars and a liquid feed of 15 ml/min.

The resultant product was tested according to USP XX dissolution procedure, i.e., one hour in simulated gastric fluid, then in simulated intestinal fluid,



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with the oral sustained release dosage form showing release of quinidine bisulfate in the following order:

<u>Time (hrs.)</u>	<u>Percent release</u>
1	9.9
2	19.6
4	37.3
6	58.6
8	79.8
10	92.4
12	100.0

WHAT IS CLAIMED IS:

1. A sustained release oral dosage form for providing a patient with quinidine over a prolonged period of time which comprises a tablet core containing a pharmaceutically effective amount of quinidine, said tablet core coated with a sustained release polymeric coating which contains from about 5 to about 20 percent by weight polyethylene glycol component having a molecular weight of from about 500 to about 2000, and from about 80 to about 95 percent by weight polyvinyl-alcohol component comprising:

(a) about one to about ten parts by weight of a partially hydrolyzed polyvinylalcohol subcomponent having a degree of hydrolysis of about 75 to about 92 percent; and

(b) about one part by weight of a substantially completely hydrolyzed polyvinylalcohol subcomponent having a degree of hydrolysis in excess of 95%.

2. A sustained release oral dosage form of claim 1 wherein said quinidine is in the form of quinidine bisulfate.

3. A sustained release oral dosage form of claim 1 wherein said partially hydrolyzed polyvinylalcohol subcomponent has a molecular weight of from about 50,000 to about 110,000.

4. A sustained release oral dosage form of claim 1 wherein said substantially completely hydrolyzed polyvinylalcohol subcomponent has a molecular weight of from about 90,000 to about 150,000.

5. A sustained release oral dosage form of claim 1 wherein said sustained release polymeric coating comprises from about three to about seven percent by weight thereof.

6. A sustained release oral dosage form of claim 1 wherein said tablet core comprises methylcellulose and lactose granules smaller than about 12 mesh which have been compressed into tablet core.



# INTERNATIONAL SEARCH REPORT

International Application No PCT/US83/01041

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC <b>9</b> A61K 9/62      A61K 9/28      A61K 9/32 424/19		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
U.S.	424/19      424/32      424/33	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup>		
Category *	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
X	JP, A, 56-110612, published 1 September 1981 Yamanouchi Pharm. KK	1-6
x	JP, A, 55-49312, published 9 April 1980 Sankyo KK	1-6
X	JP, A, 54-28812, published 3 March 1979 Yoshitomi Pharm Ind KK	1-6
Y	JP, A, 45-1274, published 16 January 1970 Tanabe Seiyaku Co. Ltd.	1-6
X	GB, A, 1,213,348, published 25 November 1970 Boehringer Mannheim G.M.B.H.	1-6
Y	US, A, 4,330,338, published 18 May 1982 Banker	1-6
X	US, A, 4,060,598, published 29 November 1977 Groppenbacher et al.	1-6
X	US, A, 3,935,326, published 27 January 1976 Groppenbacher et al.	1-6
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: <sup>15</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search *	Date of Mailing of this International Search Report *	
17 October 1983	19 OCT 1983	
International Searching Authority *	Signature of Authorized Officer <sup>20</sup>	
ISA/US	Shep K. Rose <i>Shep K Rose</i>	



**FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**

A	US, A, 3,096,248, published 2 July 1963 Rubzki	1-6
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V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 10

**This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:**

1. ☐ Claim numbers \_\_\_\_\_, because they relate to subject matter<sup>13</sup> not required to be searched by this Authority, namely:
2. ☐ Claim numbers \_\_\_\_\_, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out<sup>13</sup>, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 11

**This International Searching Authority found multiple inventions in this international application as follows:**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international searching authority did not invite payment of any additional fee.

**Remark on Protest**

- ☐ The additional search fees were accompanied by applicant's protest.  
☐ No protest accompanied the payment of additional search fees.